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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,864	11/24/2000	David Scheinberg	D6126	4077

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/721,864	SCHEINBERG ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/29/05; 10/31/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **10/31/05** has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 2-6, 8-22.

Accordingly, claims 1, 7 are being examined.

The following are the remaining rejections.

It is noted that the 103 rejection was withdrawn, in view of the amendment, but could be reinstated if the present 112, first paragraph issue were removed.

REJECTION UNDER 112, FIRST PAGRAPH, SCOPE, NEW REJECTION

Claims 1, 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for sequentially reducing the size of a solid cancer greater than 1 mm in size, does not reasonably provide enablement for a method for sequentially reducing the size of a solid cancer greater than 1 mm in size, "until tumor growth cannot recur". The specification does not enable any person skilled

in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 7 are now amended to recite a method for sequentially reducing the size of a solid cancer greater than 1 mm in size, "until tumor growth cannot recur" comprising intravenously administering a high specific activity, from about 10 mCi/mg to about 30 mCi/mg, bismuth-213/antibody construct, with repeating administration, wherein each repetition kills an additional layer of tumor cells thereby sequentially reducing the size of the solid tumor until tumor growth cannot recur.

The specification calculates that **37% or 99% of patients would achieve a 5-year disease-free survival, if treatment potency was such that 10^5 or 10^7, respectively, tumor cells could be reduced to 1 tumor cell** (emphasis added) (p.19, lines 18-21, bridging p. 20). The specification discloses that if in the same patient population, treatment reduced the total number of cells to 10 from 10^5 cells, only 5 in every 100,000 would be cured (p.20, lines 2-4).

In other words, even a single tumor cell escaped from being kill could lead to recurrence after a 5-year disease-free survival.

The specification further discloses in Example 13, on pages 44-45, that under four daily doses of B-213-antibody conjugate, the tumor-free survival time for the LNCaP xenografted mice is 33 or 54 days (p.44).

In other words, the data indicate that only after 33 or 54 days of tumor-free, the treated mice would have cancer again and die.

The specification discloses that one of the minimum requirement to achieve reliable cell killing depends on the number of receptor targets on the target cell (p.15). The specification further hypothesizes that since there are 10,000 possible sites per cell in leukemia, then 2 atoms will reach the cell and over 3 hours one will decay with an alpha into the cell and one, away form the cell, on average, and thus the minimum specific activity of about 10 mCi/mg is necessary (p.16).

One cannot extrapolate the teaching in the specification to the scope of the claims, because one cannot predict that the treated subject would not have cancer recurrence.

Even with repeated administration of the B-213-antibody conjugate, one cannot predict that recurrence would not occur, because one cannot predict whether every single cancer cell from the treated large solid tumors greater than 1 mm in size would be killed by the B-213-antibody conjugate, such that recurrence of cancer cannot occur, in view that even a single cancer cell escaped from being killed could lead to recurrence of cancer, as indicated by Applicant. Similarly, one cannot predict how many cancer cells actually could escape from being killed by the claimed conjugate, such that recurrence would not occur after a 5-year cancer-free condition, in view that only 10 escaped cancer cells could lead to recurrence of cancer in 99,995 patients from a total of 100,000 patients, as indicated by Applicant .

One cannot predict whether every single cancer cell, especially from a large solid tumor of greater than 1 mm in size would escape from being killed by the claimed antibody conjugate, nor how many cancer cells actually could escape

from being killed by the claimed conjugate, because one cannot predict whether every single target cancer cell would have adequate amount of antigen on cell surface, such that an adequate amount of alpha particle from the claimed antibody conjugate could be delivered into the target cell to effectively kill the target cell, nor the number of cancer cells, that would have adequate amount of antigen on cell surface.

It is well known in the art that cancer antigens are heterogeneous, and that the amount or level of antigens expressed on cancer cell surface could vary significantly in different individual cancer cells. For example, Greiner J W et al, 1987, J lab clin med, 109(3): 244-61, teach that as early as 1954, the existence of distinct structures in different areas of a single mammary tumor was documented, and that in mammary cancer, the tumor antigens, as detected by three different monoclonal antibodies, could be present in some areas, but not detectable in an adjacent area from a single breast cancer population (p.249). Hager J C et al, Cancer Res, 1982, 42 (11): 4325-9, teach that the mouse mammary tumors are heterogenous in expression of the tumor virus-associated cell surface antigens, with different expression in different areas of the same mammary tumor, and that heterogeneity in antigen expression has been reported in other tumor systems as well (abstract, p.4328, first column). Hager J C et al also teach that the data suggest that the antigenic heterogeneity in the tumors reflects the existence of cells within them that differ in both expression of viral tumor antigens and in their response to inducers of viral antigen synthesis (abstract). Kemshead J T et al, 1982, Brain res, 236 (2): 451-61, teach that in fresh neuronal tumor cells, although

approximately 80% of tumors are Thy-1+ (essentially 100% of cells in these being positive), there are considerable differences in the intensity of labeling in immunofluorescence between different tumors (abstract). In other words, not only there are difference in the amount of the expressed antigen Thy-1+ in different tumors, but not every single tumor cell expresses the antigen Thy-1+.

Thus, in view of such antigen heterogeneity from a single tumor, one cannot predict whether every single target cancer cell would have adequate amount of antigen on cell surface, such that an adequate amount of alpha particle from the claimed antibody conjugate could be delivered into the target cell to effectively kill the target cell, nor the number of cancer cells, that would have adequate amount of antigen on cell surface.

In view of such unpredictability of the number or level of antigens of each individual cancer cell, due to the well known antigen heterogeneity, supra, and in view that one of the minimum requirements to achieve reliable cell killing depends on the number of receptor targets on the target cell, as clearly stated by Applicant in the specification, one cannot predict that that the treated subject would not have cancer recurrence.

Further, it is well known in the art that cancer recurrence is a common, wide spread problem in cancer therapy. For example, Smith, B D, 2001, Annals Otology, rhinology, and laryngology, 110 (3): 221-8, teach that despite optimal treatment with surgery, irradiation, and chemotherapy, head, and neck squamous cell carcinoma recurrence and progression remains a common and challenging oncological problem

(abstract, and p.221, first column). Similarly, Friedel G et al, 1994, Minimally invasive therapy, 3(3): 169-172, teach that cancer recurrence is a common problem with carcinoma invading the pleural surface (abstract, and p.171, second column).

In view that cancer recurrence is such a commonly occurring phenomena, one cannot predict that the claimed method would prevent tumor growth recurrence.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Moreover, It is noted that a tumor encompasses any enlargement or abnormal growth, which is not necessarily cancerous, for example, cystic of the pancreas, splenic tumor or enlargement of the spleen, etc... (Stedman's medical dictionary, 25th ed, 1990, p.1652-1653).

It is not clear how one can successfully use the claimed method, in view of a lack of disclosure of which antigens are specific for these numerous non-cancerous tumors to be treated.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Respectfully,

MINH TAM DAVIS

February 01, 2006